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10/719,007	11/20/2003	Randolph Mellus Johnson	DURE-007CON2	9101

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,007	JOHNSON ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-56,58-67,69-72,74-81 and 83-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-56,58-67,69-72,74-81 and 83-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged of applicants' amendment filed 11/30/2009.

Claims 57, 68, 73, 82, 92-99 have been canceled.

Claims 48-56, 58-67, 69-72, 74-81, 83-91 are pending and included in the prosecution.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 48-56, 58-67, 69-72, 74-81, 83-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article "Analgesia and sedation with sufentanil in intensive care medicine" by Wappler et al. combined with article "Long term spinal therapy in terminally ill cancer patients" by Wagemans et al., Peterson et al. (US 6,524,305) and Nelson et al. (US 5,980,927).

Applicants claim

Currently amended claim 48 recites: a method for providing analgesia in a subject, said method comprising systemically administering a composition comprising sufentanil to the subject, wherein the sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml, and further wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system for 48 hours or more at a low volume rate of from about 0.01 µl/day to about 2 ml/day and is sufficient to provide analgesia in the subject.

Currently amended claim 63 recites a method for providing analgesia in a subject, said method comprising systemically administering to the subject a composition comprising sufentanil, wherein said sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml or greater, and further wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system at a low volume rate of from about 0.01 µl/day to about 2 ml/day and is sufficient to provide analgesia in the subject.

Currently amended claim 84 recites a method for providing analgesia in a subject, said method comprising systemically administering to the subject a composition comprising sufentanil, wherein the composition is administered to the subject using an implantable convective delivery system, the composition is delivered from the system for 48 hours or more at a low volume rate from about 0.1 µl/day to about 2 ml/day and is sufficient to deliver from about 0.01 µg/hour to about 200 µg/hour of the sufentanil to the subject, and further wherein said amount of delivered sufentanil is sufficient to establish a systemic analgesic effect in the subject.

Determining the scope and contents of the prior art *(MPEP § 2141.01)*

Wappler teaches that the administration of sufentanil is suitable for intensive care patients for systemic sedation and analgesia without significant respiratory depression during spontaneous breathing. Sufentanil continuous infusion was provided in a dose between 0.075 to 2.5 µg/kg/hr with median of 0.6 µg/kg/hr. See 1st, 2nd and 5th pages of the translation. For the average person weighing 60 kg, the dose disclosed by Wappler that induces systemic analgesia will ranges from 4.5 µg/hr to 150 µg/hr, which is 98-3600 µg/day, i.e. 0.098 to 3.6 mg/day. Present claims 48 and 63 recite 0.5-500 mg/ml, and recite from 0.01 µl/day to 2 ml/day. This means if average of 250.25 mg delivered at the lowest delivery rate of 0.01 µl/day, then low delivery rate as low as 0.0025 mg/day to 1000 mg/day if delivery rate is 2 ml/day, i.e. 2.5-1000,000 µg/day. Present claim 84 recites 0.01 µg/hour to about 200 µg/hour. Therefore, the claimed delivery rates of sufentanil are taught by the reference, and the claimed delivery rates disclosed by the reference falls within the broad claimed delivery rates.

Although Wappler teaches the same sufentanil delivery rates as the instantly claimed, however the reference does not teach delivery of sufentanil using implantable convective devices that deliver from 0.01 µl/day to 2ml/day to provide analgesia for prolonged periods.

Wagemans et al. teach long-term opioid therapy with minimal side effects and efficacy throughout the body and for different types of pain, i.e. systemic, with sufentanil preferred analgesic (see the entire document, especially the abstract). The analgesia is

achieved by systemic absorption of the opioid (page 72, left column, last paragraph). The opioid is administered in its minimal effective dose (table 2, page 72). The analgesic is administered by implanted infusion pump for months or years and provides constant infusion rate (page 73, left column, second paragraph). The reference further suggested physician can manage the patient's analgesic requirement (page 73, right column, last paragraph).

Peterson teaches implantable osmotic delivery system flow modulator assembly (convective device) that enhances performance of implantable osmotic devices and reduced the amount of wasted beneficial agents (abstract; col.3, lines 63-65; col.4, lines 19-20; col.11, lines 26-28; col.12, lines 38-42). The delivery system provides flow of beneficial agent between 0.02 to 50 µl/day and suitable to deliver analgesics (col.11, lines 20-23; col.13, line 65). Table I shows pumping of the beneficial agents in mg/day and amount delivered for year.

Nelson teaches prolonged delivery of sufentanil by implanted devices over periods extends up to one year (abstract; col.2, lines 39-41). Table I of the reference teaches that loading dose sufficient for long period administration, e.g. six month dose, can be calculated if the daily dose is known.

Ascertaining the differences between the prior art and the claims at issue and resolving the level of ordinary skill in the pertinent art (MPEP § 2141.012)

Therefore, at the time of the invention, it was well known to administer sufentanil in a continuous manner at a daily dose of 98-3600 µg/day, i.e. 0.098 to 3.6 mg/day, to induce analgesia as taught by Wappler. It was further known that sufentanil is the preferred analgesic for long-term opioid therapy and can be administered in the minimal effective dose for months or years by implantable pumps as taught by Wagemans. Wagemans further suggested physician can manage the patient's analgesic requirement.

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide systemic analgesia using sufentanil delivered continuously at concentration of 4.5 µg/hr to 150 µg/hr, i.e. 98-3600 µg/day, as disclosed by Wappler and deliver sufentanil using implantable infusion pump disclosed by Wagemans. One would have been motivated to do so because Wagemans teaches that implanted infusion pump is suitable for long term opioid delivery and can delivers sufentanil for months or years and provides constant infusion rate, as presently claimed. One would have reasonably expected success of providing continuous analgesia for prolonged period of times up to years with delivery rate of sufentanil from 4.5 µg/hr to 150 µg/hr.

Further, because both of Wappler and Wagemans recognized that delivery of continuous analgesia for long time was demanded, and Wagemans suggested implanted infusion pump for prolonged delivery of small dose, therefore, one having ordinary skill in the art at the time of the invention would have been motivated to use the implantable pump disclosed by Peterson because Peterson shows that implantable

osmotic delivery system can deliver active agent including analgesics for years at a low rate of 0.02 to 50 µl/day with enhanced-performing implantable osmotic devices and with reduction of the waste of beneficial agent. One would have reasonably expected inducing analgesia using implanted infusion pump that delivers low rate loaded with minimal analgesic dose of sufentanil that delivers 98-3600 µg/day from pump that provides low rate of delivery of 0.02 to 50 µl/day for long time. Therefore, at the time of the invention, applicant claim low delivery rates between 0.01 µl/day to 2ml/day, which is the selection of the delivery rate taught by Peterson.

Additionally, one having ordinary skill in the art would have been able to calculate the analgesic dose of sufentanil delivered from implantable device as disclosed by Nelson. Nelson showed that it is possible to calculate the dose to be loaded in an implantable device if the daily dose and period of administration are known.

Therefore, at the time of the invention, one skilled in the art would be motivated to induce analgesia using the present method because the prior art teaches the use of sufentanil for prolonged delivery at minimal doses, and further at low delivery rates from implantable devices.

All the elements of the claimed method were known at the time of the invention and further the cited references provided motivation to combine them. It has been held that "When a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR Int 'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (quoting *Sakraida v. AG Pro, Inc.,* 425 U.S. 273,282 (1976)).

"When the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions."

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been *prima facie* obvious within the meaning of 35 U.S.C. 103(a).

Response to Arguments

5. Applicant's arguments filed 11/30/3009 have been fully considered but they are not persuasive.

Applicants argue that the combination of Wappler, Wagemans, Peterson and Nelson fails to teach or suggest each and every claim element. The methods of independent claims 48 and 63 as currently amended each require systemically administering a composition comprising sufentanil to a subject, wherein the sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml. The only weight-based delivery rates relied on by the Office are provided in Wappler and Nelson. Wappler's teaching of "98-3600 μg/day, i.e. 0.098 to 3.6 mg/day" does not amount to a teaching to administer a composition having the concentration range set forth in the claims. In other words, a teaching to deliver 0.098 to 3.6 mg/day of sufentanil tells one of ordinary skill in the art nothing about the concentration (in mg/ml) of sufentanil in the composition. Nelson does not remedy the deficiencies in Wappler with respect to the claimed concentration of sufentanil in the composition. The cited

portions of Nelson relied on by the Office refer to fentanyl and not to sufentanil. Accordingly, Nelson cannot cure the deficiencies in Wappler with respect to the claimed concentration of sufentanil in the composition. As neither Wagemans nor Peterson disclose any specific sufentanil concentrations, these references also fail to cure the identified deficiencies in Wappler.

In response to this argument, it is argued that Wappler clearly teaches that the administration of sufentanil is suitable for intensive care patients for **systemic sedation and analgesia without significant respiratory depression during spontaneous breathing.** Therefore systemic administration is taught by Wappler. Further the daily dose in mg/ml as calculated reads on the claims. Sufentanil continuous infusion was provided in a dose between 0.075 to 2.5 µg/kg/hr with median of 0.6 µg/kg/hr. For the average person weighing 60 kg, the dose disclosed by Wappler that induces systemic analgesia will ranges from 4.5 µg/hr to 150 µg/hr, which is 98-3600 µg/day, i.e. 0.098 to 3.6 mg/day. Present claims 48 and 63 recite 0.5-500 mg/ml, and recites from 0.01µl/day to 2 ml/day. This means if average of 250.25 mg delivered at the lowest delivery rate of 0.01 µl/day, then low delivery rate as low as 0.0025 mg/day to 1000 mg/day if delivery rate is 2 ml/day, i.e. 2.5-1000,000 µg/day. Present claim 84 recites 0.01 µg/hour to about 200 µg/hour. In other words, Wappler teaches delivery of the same amount of sufentanil per day, and teaches the same delivery rate, and this suggests the same total concentration in device as instantly claimed. Therefore, the claimed delivery rates of sufentanil are taught by the Wappler, and the claimed delivery rates disclosed by the reference fall within the broad claimed delivery rates. Wappler teaches low dosage and

dose is expected to be less for debilitating or patients with lighter weights. Wappler further suggested that dose can be adjusted according to patient requirement, i.e. can be reduced to the claimed ranges. Both references disclose un-interrupted delivery of the analgesics once the desired level to induce analgesia is achieved. Further, Peterson teaches the low delivery volume rate for long time. The implantable devices that deliver low volume for extended periods were known at the time of the invention and taught by Peterson. Further Peterson suggested delivery of analgesics, and Wagemans desired long term opioid therapy. Therefore, at the time of the invention, one having ordinary skill in the art would have used the implantable osmotic device disclosed by Peterson to deliver sufentanil in the doses disclosed by the combination of Wappler and Wagemans. Nelson teaches prolonged delivery of analgesics by implanted devices over periods extends up to one year. Table I of the reference teaches that loading dose sufficient for long period administration, e.g. six month dose, can be calculated if the daily dose is known and this would suggest o one having ordinary skill in the art that it is possible to calculate the required does of sufentanil to be loaded in implantable device for long term therapy. Nelson exemplified fentanyl, however, teaches prolonged delivery of analgesics and recommended sufentanil because of its potency.

Applicants argue that no apparent reason to combine the disclosed delivery rates of Wappler in the continuous infusion method described by Wagemans. This is because Wagemans solves the problem of providing analgesia in a subject in a completely different manner than that employed by Wappler. Wagemans describes spinal, i.e., local

administration of opioids directly to the receptors it will act upon, and not systemic administration. Wagemans states: "The normal dosage of spinal opioids is considerably lower than systemic opioid dosage, therefore producing fewer side effects." Wagemans indicates that in epidural administration "systemic adsorption" occurs in addition to penetration of the dura matter and arachnoid. Wagemans indicates the advantages of spinal administration. Wappler suggests that the drug is administered intravenously, i.e., systemically, in contrast to local delivery taught by Wagemans.

In response to this argument, the present claims are directed to method of inducing systemic analgesia and recite only one step of the method, which is systemic administration of sufentanil by implantable device. The claims do not require any specific site of administration, therefore, epidural and administration is encompassed by the claims. Wagemans teaches long-term opioid **profound therapy**, i.e. not only at the site of administration, with minimal side effects and efficacy throughout the body and for different types of pain, and further teaches sufentanil is a preferred analgesic in minimal effective dose. Wagemans teaches **systemic absorption of opioids delivered by epidural and intrathecal** routes, page 72, right column, first full paragraphs. Wagemans discussed both local and systemic administration of opioids. Wagemans teaches local delivery that provides both systemic and local analgesic effects by teaching "**efficacy throughout the body and for different types of pain are important advantages**." Although Wagemans teaches advantages of local administration, the reference further teaches in page 72, right column that "Both epidural and intrathecal routes have advantages and disadvantages". Therefore, every

route of administration, either local or systemic has its own advantage and disadvantage. It is further argued that, even with local administration, **it is inevitable to have some opioid absorbed systemically from the local administration site to provide systemic effect**. Additionally, Wagemans teaches delivery by implanted infusion pump for months or years and provides constant infusion. Therefore, constant infusion for long periods of minimal effective dose of sufentanil for systemic effect is taught by Wagemans. Wappler disclosed continuous pump infusion. Both Wagemans and Wappler teach method of delivery of sufentanil by infusion and both teach systemic delivery, however, Wappler preferred intravenous infusion and Wagemans preferred spinal infusion. The present claims are not directed to any specific site of delivery of sufentanil. The disclosed examples and preferred embodiment do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Applicants argue that the combination of Wappler and Wagemans fails to render the claims prima facie obvious.

In response to this argument, it is argued that the present claimed method as a whole is taught by the combination of the cited prior art as currently rejected. Therefore, the invention as a whole is taught by the combination of the cited prior art. A prima facie case of obviousness has been established.

Applicants argue that Nelson teaches away from the combination with Wappler and teaches away from the claimed invention. Nelson provides a device and method for administering an analgesic directly to the neuraxis of an organism. Nelson describes problems associated with various methods of systemic administration of opioid analgesics. By describing the various problems associated with systemic administration of opioid analgesics, and by offering its own device and method as an alternative, Nelson clearly teaches away from the systemic administration of opioid analgesics. In contrast to Nelson, Wappler suggests systemic administration of drug as discussed above. As such, one of ordinary skill in the art would be directed away from the combination with Wappler given Nelson's teaching that the systemic administration of these analgesics is undesirable. Furthermore, the claims as currently amended specifically recite "systemically administering" a composition.

In response to this argument, it is argued that Nelson teaches treatment of chronic pain, and does not limit the site of pain. Therefore, any kind of pain at any part of the body will be treated by the implantable device of Nelson. Wappler disclosed continuous delivery by i.v. Both Nelson and Wappler teach method of continuous prolonged delivery of sufentanil and both teach systemic delivery. It is further argued that, **even with local administration, it is inevitable to have some opioid absorbed systemically from the local administration site to provide systemic effect**. Nelson is relied upon for teaching that it is possible to calculate the dose to be loaded in an implantable device if the daily dose and period of administration are known. The present claims are not directed to any specific site for delivery of sufentanil. The disclosed

examples and preferred embodiment do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). Therefore, Nelson does not teach away from Wappler, nor deter one having ordinary skill in the art to combine Nelson with Wappler and Wagemans. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." In re Gurley, 27 F.3d 551,553 (Fed. Cir. 1994).

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Isis A Ghali/
Primary Examiner, Art Unit 1611

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